determining the effect of the agent on the SCD1 activity in the subject, wherein a reduction in SCD1 activity caused by the agent indicates that the agent can increase insulin sensitivity in the subject.

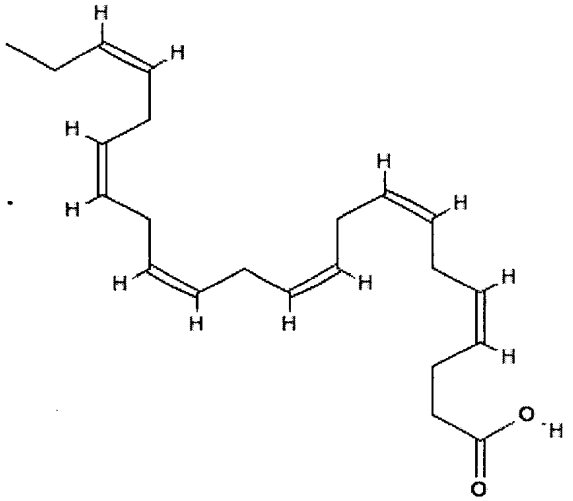
REMARKS

In an Office Action mailed November 27, 2006, the Examiner rejected the claims under the judicially created doctrine of obviousness-type double patenting and rejected the claims under 35 U.S.C. §§ 112 and 102. Applicants respond to each of the Examiner's rejections below. In view of the amendments noted above and the remarks presented herein, Applicants respectfully request reconsideration of the merits of this application.

Telephonic Interview

Applicants and the undersigned thank Examiner Schlientz for his time during a December 1, 2006 telephonic interview. During the interview, the Examiner and the undersigned discussed the structure of dodecahexaenoic acid (DHA). The Examiner noted that DHA is indefinite because it does not correspond to a structure having six double bonds in a twelve carbon chain. Applicants are grateful that the Examiner has noted this anomaly, as confusion exists in the art as to the structure/name of DHA.

Despite its name, DHA is not a C12:6 compound. For the Examiner's convenience, Applicants enclose four (4) documents in which skilled artisans refer to DHA as a C22:6 compound, which Applicants submit is represented by the following structure:



See, Body D, "The composition of orange roughy (*Hoplostethus atlanticus*) roe lipids," J. Sci. Food Agric. 36:679-684 (2006); McDonald G, *et al.*, "Seasonal changes in Hoki (*Macruronus novaezelandaie*) - implications for quality and yield," J. Aquat. Food Prod. Tech. 11:35-51 (2002); Osterroht C, "Extraction of dissolved fatty acids from sea water," Fresenius' J. Anal. Chem. 345: 773-779 (1993); and Pikul J, *et al.*, "Relative role of phospholipids, triacylglycerols, and cholesterol esters on malonaldehyde formation in fat extracted from chicken meat," J. Food Sci. 49: 704-708 (1984). Applicants trust that these remarks, the structure shown above and the cited documents clarify the nature of the intended molecule.

Rejections Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner provisionally rejected Claims 1-5 and 7-10 under the judicially created doctrine of obviousness-type double patenting over Claims 1-9 of US Patent Application No. 10/094,841 by Ntambi *et al.* The Examiner alleged that Ntambi *et al.* disclose methods of controlling body fat in human or non-human subjects by reducing SCD1 enzymatic activity that inherently render obvious methods of increasing insulin sensitivity by reducing SCD1 enzymatic activity. Applicants amend Claim 1 to recite an additional step of "measuring insulin sensitivity and observing an increase in insulin sensitivity following a reduction in SCD1 activity." Support for this amendment is located in Example 2, paragraph [00120]. One skilled in the art had no reason to expect that reducing or inhibiting SCD1 activity would increase insulin sensitivity and therefore had no a priori reason to observe (*i.e.* measure) an increase in insulin sensitivity following a reduction in SCD1 activity. As such, the new step is not obvious in view of Ntambi *et al.* In view of these remarks and the amendment noted above, Applicants respectfully request reconsideration of this rejection as applied to Claims 1-5 and 7-10.

The Examiner also provisionally rejected Claims 1 and 8-9 under the judicially created doctrine of obviousness-type double patenting over Claim 48 of US Patent Application No. 11/195,561 by Hayden *et al.* The Examiner alleged that Hayden *et al.* disclose methods of treating diabetes and insulin resistance in an individual by inhibiting SCD1 protein expression or activity that render obvious methods of increasing insulin sensitivity by inhibiting SCD1 activity. As noted above, Applicants amend Claim 1 to recite

the additional step of "measuring insulin sensitivity and observing an increase in insulin sensitivity following a reduction in SCD1 activity." Again, one skilled in the art had no reason to expect that reducing or inhibiting SCD1 activity would increase insulin sensitivity or to observe (*i.e.* measure) an increase in insulin sensitivity following a reduction in SCD1 activity. As such, the new step is not obvious in view of Hayden *et al.* In view of these remarks and the amendment noted above, Applicants respectfully request reconsideration of this rejection as applied to Claims 1 and 8-9.

Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner rejected Claims 1 and 7-11 under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. The Examiner alleged that although the specification describes assays to identify compounds that reduce SCD1 activity, it fails to adequately provide guidance as to which compounds should be screened. In support of this rejection, the Examiner cited *University of Rochester v. G.D. Searle & Co.*, 375 F.3d 1303 (Fed. Cir. 2004).

The written description issue of the patent ('850 patent) cited in *University of Rochester* is distinguishable from the written description rejection of the application. In *University of Rochester*, the record stated that beyond using the term, "non-steroidal compound," the '850 patent "neither discloses any such compound nor provides any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research." In contrast to *University of Rochester*, Applicants disclose the use of SCD1 knockout (SCD1 -/-) mice, in which effects of a complete absence of SCD1 were actually described. Deletion of SCD1 in SCD1 -/- mice necessarily represents SCD1 inhibition taken to an extreme. Consequently, the results described in the application represent neither mere side-effects nor hypothetical effects of inhibiting SCD1 with various compounds, but rather effects unambiguously associated with SCD1 inhibition.

Moreover, the written description requirement under § 112 only requires a detailed description of that which is new (*see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986)). In the application, Applicants described that inhibition of SCD1, by deletion of the gene, resulted in increased insulin sensitivity independent of the mechanism of SCD1-inhibiting activity. As this link was previously unknown in the art, Applicants are entitled to a broad scope of protection with respect to compounds that inhibit SCD1.

In discussing compounds that could be used to inhibit SCD1 activity, the Examiner alleged that the application lacks information to direct one skilled in the art to compounds that have the desired characteristic of reducing SCD1 activity. Applicants respectfully disagree and note that, in contrast to the facts of *University of Rochester*, actual compounds for inhibiting SCD1 activity are described in the application. In fact, an entire section of the application is directed to what SCD1 biological activity means and to compounds that inhibit SCD1 biological activity. *See, e.g.*, paragraphs [0026]-[0040]. Likewise, paragraph [0024] discloses that SCD1 activity can be lowered through genetic manipulation or through modulators of SCD1 activity.

Paragraph [0027] then describes three ways to reduce SCD1 activity. First, one skilled in the art can reduce SCD1 protein level, e.g., by increasing SCD1 degradation or by decreasing SCD1 synthesis (i.e. at the transcription or translational level) (paragraphs [0028]-[0029]). With respect to inhibiting transcription, paragraph [0028] describes transcription factors involved in SCD1 regulation and three classes of inhibitors (*e.g.*, thiazoladine compounds, leptin and polyunsaturated fatty acids) that can be used with the methods of the present invention. With respect to inhibiting translation, paragraph [0029] describes antisense technology. As noted in paragraphs [0025] and [0029]-[0031], one skilled in the art is familiar with antisense technology and is familiar with the nucleic acid sequences of not only SCD1, but also of cytochrome b_5, NADH (P)-cytochrome b_5 reductase and terminal cyanide-sensitive reductase.

Second, one skilled in the art can inhibit SCD1 enzymatic activity. Paragraph [0032] describes compounds and their derivatives suitable for inhibiting SCD1 enzymatic activity. The structure of these compounds are well-known to one skilled in the art and need not be described in exhaustive detail in the application. Alternatively, and as noted in paragraphs [0025] and [0035], one skilled in the art can inhibit SCD1 enzymatic activity with antibodies to SCD1. Like antisense technology, one skilled is familiar with methods for making antibodies and is familiar with the amino acid sequences of not only SCD1, but also cytochrome b_5, NADH (P)-cytochrome b_5 reductase and terminal cyanide-sensitive reductase are known.

Third, one skilled in the art can interfere with members of the SCD1 desaturase system. Specifically, paragraph [0036] contemplates using compounds that interfere with forming a stable complex between cytochrome b_5, NADH (P)-cytochrome b_5 reductase and

terminal cyanide-sensitive reductase, of which the amino acid and nucleic acids sequences are well-known to one skilled in the art. As such, Applicants submit that the application adequately describes methods and agents to reduce/inhibit SCD1.

In view of these remarks, Applicants respectfully request reconsideration of this rejection as applied to Claims 1 and 7-11.

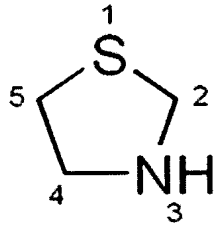
The Examiner also rejected Claims 1 and 7-11 under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. The Examiner alleged that one skilled in the art would practice undue experimentation to determine which compounds for reducing SCD1 activity should be screened. Applicants respectfully disagree.

The pending claims are not directed to methods of screening compounds, as Claims 12-13 are withdrawn from prosecution. The pending claims are directed to increasing insulin sensitivity by reducing SDC1 activity. Agents to reduce SCD1 activity, including, but not limited to, SCD1 antisense molecules, SCD1 antibodies, thiazoladinediones and polyunsaturated fatty acids, are known to one skilled in the art and are described in the application. These agents have known structures and have been administered to human and non-humans. *See, e.g.*, the documents cited by the Examiner in support of rejections under 35 U.S.C. § 102(b). Furthermore, methods of making antibodies to proteins and methods of making antisense molecules to nucleic acids are well-known to one skilled in the art. Given that the methods of making these types of inhibitors are well-known and that the structure of the targets (i.e. SCD1, cytochrome b_5, a NADH-cytochrome b_5 reductase and terminal cyanide-sensitive desaturase) are well-known, one skilled in the art would be required to practice no more than routine procedures to obtain the inhibitors and to test them. The Examiner himself acknowledges that SCD1 and methods/agents to reduce SDC1 activity are well-known in the art. *See* pp. 8 and 16-19 of the Office Action.

Accordingly, the application enables one skilled in the art to practice the claimed invention. In view of these remarks, Applicants respectfully request reconsideration of this rejection as applied to Claims 1 and 7-11.

The Examiner also rejected Claims 1-4 under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. The Examiner alleged that although the specification enables using thiazoladinediones (also called glitzazones in the art) such as BRL49653, Pioglitazone, Ciglitazone, Englitazone and Troglitazone, one skilled in the art would be required to practice undue experimentation for any thiazoladinedione or for any polysaturated fatty acids. With respect to thiazoladinediones, Applicants disclosed the entire class of thiazoladinedione compounds available to one skilled in the art (note, BRL49653 is now sold under the name, Rosiglitazone). As a class, one skilled in the art understands that thiazoladinediones are organic compounds with a thiazolidine ring. The thiazolidine ring is a

five-membered, saturated ring with an amine group and a sulfide group in the 1 and 3 positions, which is shown as follows:



Likewise, the Examiner failed to show any example of another thiazoladinedione other than those recited in the application. Given the list of thiazoladinediones supplied in the application and the general structural requirements of a thiazoladinedione note above, Applicants submit that the application enables the use of thiazoladinediones generally.

With respect to polysaturated fatty acids, Applicants note that Claim 4 contains a typographical error and amend it to recite that the fatty acids are "polyunsaturated" fatty acids. Support for this amendment is found in Claim 6, as well as paragraphs [0028] and [0032]-[0033] of the application. In view of these remarks and the amendment noted above, Applicants respectfully request reconsideration of this rejection as applied to Claims 1-4.

The Examiner also rejected Claim 11 under 35 U.S.C. § 112, first paragraph for failing to comply with the enablement requirement. The Examiner alleged that the specification does not enable claims directed to increasing insulin sensitivity by inhibiting cytochrome b_5, NADH-cytochrome b_5 reductase or terminal cyanide-sensitive desaturases. It is settled law that an invention can be enabled even if certain embodiments are not operative. The standard is whether one skilled in the art could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *See* MPEP 2164.08(b), citing *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

One skilled in the art would expend little effort than is normally required in the art to increase insulin sensitivity by inhibiting cytochrome b_5, NADH-cytochrome b_5 reductase or terminal cyanide-sensitive desaturases. To determine whether a particular cytochrome b_5, NADH-cytochrome b_5 reductase or terminal cyanide-sensitive desaturase inhibitor reduces SCD1 activity, one skilled in the art only needs to administer an inhibitor of any one of the aforementioned components of the desaturase system. Because the amino acid and nucleotide sequences for these proteins were known as of the filing date, one skilled in the art is capable of making an antibody to the protein themselves or antisense molecules to the

RNA of any of them. Both are simple, routine experiments, and one skilled in the art would not consider this to be more effort that is normally required, which is the enablement standard set forth by the Federal Circuit, as discussed above. In view of these remarks, Applicants respectfully request reconsideration of this rejection as applied to Claim 11.

The Examiner also rejected Claim 4 under 35 U.S.C. § 112, first paragraph for failing to meet the written description requirement. The Examiner alleged that the specification does not support claims directed to increasing insulin sensitivity by administering a polysaturated fatty acid because the specification only discloses using polyunsaturated fatty acids. As noted above, Applicants amend Claim 4 to recite that the agent is polyunsaturated. In view of this amendment, Applicants respectfully request reconsideration of this rejection as applied to Claim 4.

Rejections Under 35 U.S.C. § 112, second paragraph

The Examiner rejected Claims 1-11 under 35 U.S.C. § 112, second paragraph for indefiniteness. The Examiner alleged that the word "sufficiently" is unclear as one skilled in art would not know to what extent SCD2 activity must be reduced to be sufficient to increase insulin sensitivity. Applicants delete the word "sufficiently" from Claim 1. In view of this amendment, Applicants respectfully request reconsideration of this rejection as applied to Claims 1-11.

The Examiner also rejected Claims 1-3, 8 and 11 under 35 U.S.C. § 112, second paragraph for being incomplete. The Examiner alleged that the claims fail to set forth an active ingredient and an active step for increasing insulin sensitivity. Applicants amend Claim 1 to recite the step of "administering an agent." Applicants also amend Claims 2-3, 8 and 11 to recite "the agent" so that these claims are commensurate with Claim 1. In view of these amendments, Applicants respectfully request reconsideration of the this rejection as applied to Claims 1-3, 8 and 11.

The Examiner also rejected Claim 6 under 35 U.S.C. § 112, second paragraph because the phrase "polyunsaturated fatty acid" lacks antecedent basis. Claim 6 depends from Claim 4, which now recites polyunsaturated fatty acid. In view of this amendment, Applicants respectfully request reconsideration of this rejection as applied to Claim 6.

The Examiner also rejected Claim 7 under 35 U.S.C. § 112, second paragraph because the phrase "SCD1 protein level is reduced" lacks antecedent basis. Applicants amend Claim

7 to delete the phrase "SCD1 protein level is reduced" and to depend from Claim 3 instead of Claim 1. In view of these amendments, Applicants respectfully request reconsideration of this rejection as applied to Claim 7.

The Examiner also rejected Claim 11 under 35 U.S.C. § 112, second paragraph because the phrase "the inhibitor" lacks antecedent basis. Amended Claim 11 mirrors the language of Claim 8. That is, Claim 8 now recites "the agent" instead of "the inhibitor." In view of this amendment, Applicants respectfully request reconsideration of this rejection as applied to Claim 11.

Rejections Under 35 U.S.C. § 102

The Examiner rejected Claims 1-8 and 11 under 35 U.S.C. § 102 as anticipated by Lehmann J, *et al.*, "An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma)," J. Biol. Chem. 270:12953-12956 (1995); Ntambi J, *et al.*, "A model cell line to study regulation of stearoyl-CoA desaturase gene 1 expression by insulin and polyunsaturated fatty acids," Biochem. Biophys. Res. Commun. 220:990-995 (1996) (hereinafter Ntambi I); US Patent No. 7,132,529 to Crooke & Graham; US Published Patent Application No. 2003/0064950 by Ntambi *et al.* (hereinafter Ntambi II); and US Published Patent Application No. 2003/0157552 by Hayden *et al.*

The Examiner alleged that these documents anticipate the pending claims by disclosing methods of treating diabetes or insulin resistance/sensitivity by the administration of thiazoladinedione compounds (Lehmann *et al.* and Ntambi II), the administration of polyunsaturated fatty acids (Ntambi I and Ntambi II); the administration of antisense molecules (Crooke & Graham and Ntambi II); and the administration of SCD1 inhibitors (Hayden *et al.* and Ntambi II), respectively, thereby inherently increasing insulin sensitivity through inhibiting SCD1, as well as inherently inhibiting the following proteins: cytochrome b_5, NADH-cytochrome b_5 reductase and/or terminal cyanide-sensitive desaturase. Applicants respectfully disagree.

None of the cited documents anticipate the pending claims. As amended, Claim 1 recites the step of "measuring insulin sensitivity and observing an increase in insulin sensitivity following a reduction in SCD1 activity." Prior to Applicants' disclosure, one skilled in the art had no reason to expect that reducing or inhibiting SCD1 activity would result in an increase in insulin sensitivity and then to observe (i.e. measure) an increase in

insulin sensitivity following a reduction in SCD1 activity. No cited document, however, explicitly or inherently discloses this step. In view of the amendment noted above, Applicants respectfully request reconsideration of this rejection as applied to Claims 1-8 and 11.

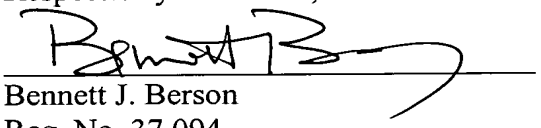
Additional Remarks

The Examiner noted that "thiazoladinedione" in Claims 4-5 is understood to be "thiazolidinedione." Both spellings are accepted in the art.

Fees

A petition for an extension of time for three months accompanies this response so that it will be deemed to have been timely filed. No other extension of time is believed due, but should any additional extension be due, in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the extension fee to Deposit Account No. 17-0055. No additional fees are believed due; however, if any fees are due, in this or any subsequent response, please charge Deposit Account 17-0055.

Respectfully submitted,



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